

# Development of zona zoster during bortezomib treatment in patients with Relapsed/Refractory multiple myeloma

*Relaps/refrakter multiple myelom hastalarında bortezomib tedavisi sırasında zona zoster gelişimi*

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## Introduction

Bortezomib, the first selective proteasome inhibitor, has demonstrated significant preclinical activity in several tumor models and a significant antitumor activity as a single agent and in combination with dexamethasone in patients with refractory or relapsed multiple myeloma [1,2]. Bortezomib is well tolerated; most side effects are only mild to moderate and are manageable [3]. The most common reported adverse events are peripheral neuropathy and thrombocytopenia. In this report, development of zona zoster infection in two of our five patients with refractory/relapsed multiple myeloma during bortezomib treatment is described and the possible association between bortezomib treatment and zona zoster is discussed with a review of the literature.

## Case Reports

**Case 1.** A 68-year-old female patient received six courses of bortezomib plus dexamethasone for relapsed myeloma while using thalidomide as second-line treatment. She admitted with the complaints of shingles, burning and pain after the second course. Diagnosis of zona zoster (grade 3) was apparent but the management of pain lasted for more than three weeks and the use of epidural patient-controlled anesthesia was required. This was the first attack of herpes zoster in this patient.

**Case 2.** A 51-year-old male patient received six courses of bortezomib plus dexamethasone after relapsing from tandem

autologous peripheral stem cell transplantation. After the second course, grade 2 zona zoster was diagnosed and the therapy was withheld for two weeks. Herpes zoster infection was not observed in this patient even during autologous peripheral stem cell transplantation and this was the first attack.

## Discussion

Nuclear transcription factor kappa B (NFκB) is a central mediator of the immune response. It is a multi-subunit transcription factor that can rapidly activate transcription of various inflammatory cytokines, adhesion molecules, and chemokines [1,2]. The major biological effect of bortezomib is the inhibition of the NFκB, with subsequent inhibition of the growth of tumor cells, induction of apoptosis, and inhibition of angiogenesis and of cellular adhesion.

Brown et al. [3] demonstrated that bortezomib induced very early, early and late gene expression in vitro belonging to Kaposi's sarcoma-associated herpes virus, which appears as a latent infection in two lymphoma cell lines. Upon their findings, the investigators expressed that signaling pathways were regulated by proteasome for the activation of this latent infection. Similar mechanisms could take part in the reactivation of herpes zoster infection, which is another latent herpes virus infection.

Kroger et al. [4] reported their observation of herpes zoster infection in three (17%) of 18 patients who received bortezomib after dose-reduced allogeneic stem cell transplantation. Certainly, since herpes zoster infections might be observed frequently after allogeneic stem cell transplantations, it is possible

that use of bortezomib predisposes to the development of herpes zoster infection, similar to our cases.

Actually, multiple myeloma itself could cause an immunosuppressive condition that could possibly activate latent zona zoster infection [5]. Similar to the observations in our cases, activations of zona zoster have been reported during applications of other chemotherapies in cases with multiple myeloma [6-8].

Kropff et al. [9] reported >grade 2 herpes zoster infection in two (14%) of 15 relapsed/refractory patients treated with bortezomib in combination with dexamethasone. In a recent update by San Miguel et al. [10], it was reported that some centers observed higher incidence of herpes zoster during bortezomib and dexamethasone treatment. They also reported that the use of acyclovir is advised by some centers; however, they did not specify the rate of the "higher incidence" or the centers that advise the use of anti-viral prophylaxis in their references.

In conclusion, treatment-related NF $\kappa$ B inhibition could cause reactivation of latent zona zoster infection during bortezomib treatment. Further data are required before formal recommendations can be made regarding anti-infective prophylaxis.

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